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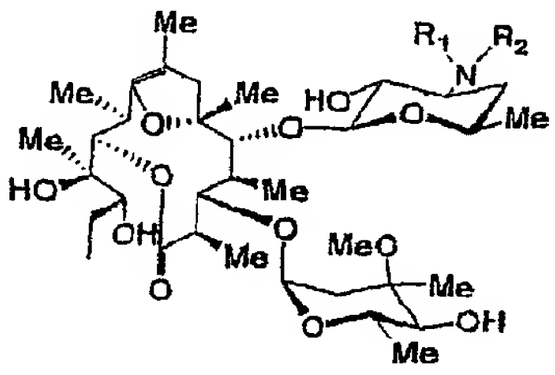
(54) NOVEL PSEUDOERYTHROMYCIN DERIVATIVES

(57) The present invention is to obtain novel anti-inflammatory agents having decreased antibacterial activity and increased anti-inflammatory action, and is pseudoerythromycin derivatives represented by the following general formula [I],



[I]

wherein R1 and R2 are same or different and each represents H, alkyl, alkynyl, acyl or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to novel pseudoerythromycin derivatives or salt thereof.

2. Description of Related Art

[0002] Erythromycin (hereinafter sometimes designates as EM) has been used for long time as 14-membered macrolide antibiotic for treatment of infectious disease caused by Gram-positive bacteria. During past ten and several years, erythromycin has known to improve long-term chronic inflammatory diseases such as diffuse panbronchiolitis and bronchial asthma, except for therapeutic action to bacterial infectious diseases. (Kudo, Shoji et al., Studies of clinical results on long term small administration of erythromycin for diffuse panbronchiolitis-Treatment results for 4 years, J. Japan. Thorac. Dis. Assoc., 25: 632-642, 1987).

[0003] Erythromycin is an antibiotic and has antibacterial action which is not always required for treatment of inflammatory diseases. Consequently, resistant bacteria are generated in patients who are administered antibiotics, as a result, it causes deterioration for treatment of infectious disease in the other occasion.

[0004] As described above, Kudo, Shoji et al. demonstrated that diffuse panbronchiolitis could be improved by long term small administration of erythromycin (Kudo, Shoji et al., Studies of clinical results on long term small administration of erythromycin for diffuse panbronchiolitis-Treatment results for 4 years, J. Japan. Thorac. Dis. Assoc., 25: 632-642, 1987).

SUMARRY AND OBJECT OF THE INVENTION

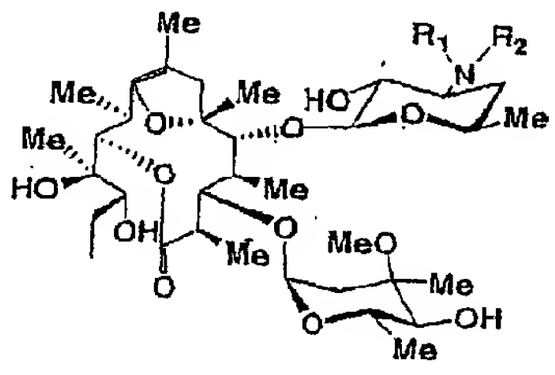
[0005] Recently, actions other than antibiotic activity of erythromycin is noted, as a result, usefulness other than pulmonary region, for example not limited in diffuse panbronchiolitis but for chronic sinusitis and Crohn's disease are reported. The mechanism of action of erythromycin for chronic disease such as diffuse panbronchiolitis is thought to be the result of original antibacterial action. Research studies are now ongoing, and indicate the antiinflammatory action mediated by immune inflammatory cells in the penumbral chronic respiratory tract inflammation.

[0006] For example, the studies indicate the regulation for migration of neutrophils to infectious region by direct action, and the regulation for migration of neutrophils or for release of active oxygen from neutrophils by indirect action through mediators or cytokines. Further, erythromycin has an action to lymphocytes, macrophages and mast cells to regulate their proliferation or cytokine production, or to induce differentiation. (Kudo, Shoji Ed., Supervisors: Shimizu, Kihachiro and Omura Satoshi "Inflammation, Immunity and Macrolides Up to Date", Iyaku Journal Inc., Osaka, 1996)

[0007] As explained above, 14-membered macrolides are thought to cure chronic respiratory diseases as a result of exhibiting immune regulation and antiinflammatory action.

[0008] We have aimed at the promoting action of erythromycin for differentiation-induction from monocyte to macrophage (N. Keicho, S. Kudoh, H. Yotsumoto, K. Akagawa, "Erythromycin promotes monocyte to macrophage differentiation", J. Antibiotics, 47, 80-89, 1994), and tried to synthesize erythromycin derivatives for the purpose of creating the derivatives having disappeared antibacterial action and enhanced promoting action for differentiation-induction.

[0009] The present invention relates to a novel pseudoerythromycin derivative represented by the general formula [I],

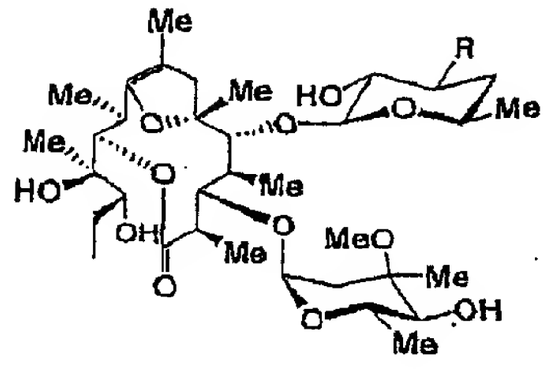


[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

[0010] Further, the present invention relates to a novel pseudoerythromycin derivative represented by the general

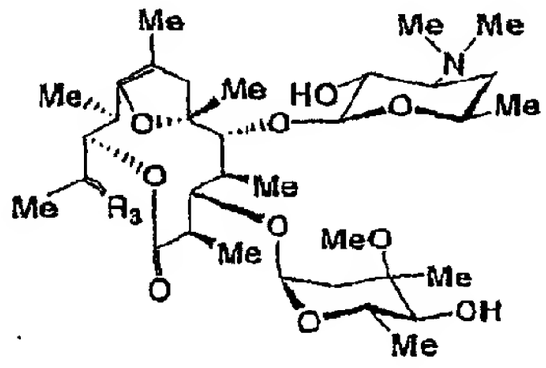
formula [II],



[II]

wherein R is heterocyclic containing N which may optionally have substituents, and Me indicates methyl.

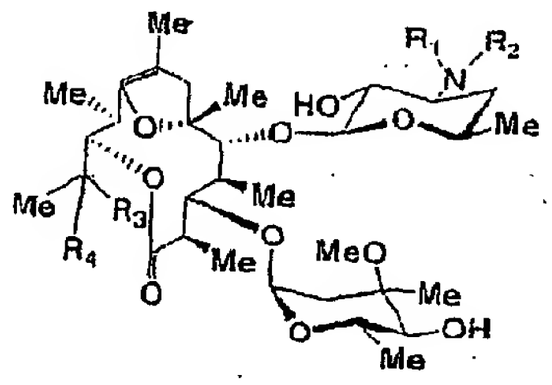
[0011] The present invention further relates to a novel pseudo erythromycin derivative represented by the general formula [III],



[III]

wherein R_3 is O or NOH, and Me indicates methyl.

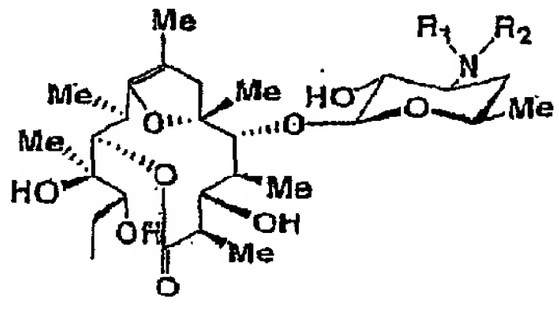
[0012] The invention further relates to a novel pseudoerythromycin derivative represented by the general formula [IV],



[IV]

wherein R_1 and R_2 are same or different and each represents H or methyl, R_3 and R_4 represent H, hydroxyl or amino, and Me indicates methyl.

[0013] The present invention further relates to a novel pseudo erythromycin derivative represented by the general formula [V],



[V]

wherein R_1 and R_2 are same or different and each represents H or methyl, and Me indicates methyl.

[0014] Synthetic methods of various erythromycin derivatives are, for example, illustrated in the synthetic scheme as shown in Fig. 1. Namely, erythromycin A is treated with ice-cold acetic acid according to the references: (a) I. O. Kibwage, R. Busson, G. Janssen, J. Hoogmartens, H. Vanderhaeghe, Translactonization of Erythromycins, J. Org. Chem., 52, 990-996, 1987, (b) H. A. Kirst, J. A. Wind, J. W. Paschal, Synthesis of Ring-Constracted Derivatives of Erythromycin, J. Org. Chem., 52, 4359-4362, 1987, introducing to erythromycin A enol ether (EM 201), subsequently refluxing in methanol with heating in the presence of potassium carbonate to introduce pseudoerythromycin A enol ether (EM701) (known compound).

[0015] The product was treated with iodine and sodium acetate according to the reference (L.A. Friberg, U.S. Patent 3,725,385) to obtain de-N-methyl-pseudoerythromycin A enol ether (EM703) (known compound). The compound was further treated with iodine and sodium methoxide to obtain bis(de-N-methyl)-pseudo erythromycin A enol ether (EM721) (novel compound). Alkylation, acylation and sulfonylation using EM703 and EM721 resulted to synthesize various derivatives through bis-de(3'-N-methyl) -3'-N-ethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM722).

[0016] The synthetic scheme of compounds of the present invention is illustrated in Fig. 1. Namely, the compounds can be obtained by the synthetic route of: erythromycin A (EMA) → erythromycin A enol ether (EM201) → pseudo-erythromycin A enol ether (EM701) → de-N-methyl-pseudoerythromycin A enol ether (EM703) → bis (de-N-methyl)-pseudoerythromycin A enol ether (EM721).

[0017] In order to confirm enhancing effect for differentiation -induction of the compounds of the present invention, the enhancing effect for differentiation-induction from human monocyte to macrophage was assayed. Method is performed as follows.

[0018] THP-1 cells were collected from cultured liquid by centrifugation, adjusted the concentration to 2×10^5 cells/ml using medium (RPMI 1640) and distributed into the 48-well plate at 500 μl/well. PMA solution 10 μl and sample solution 5μl were added in each well, stirred with mild shaking and incubated at 37 °C for 72-96 hours under 5% CO_2. Further MTT 0.5 mg/ml solution was added at 300 μl/well, and incubated at 37°C for 3 hours under 5% CO_2. Supernatant solution was suctioned using the injection tube, added DMSO 500μl using automatic continuous injector to dissolve formazan completely and transferred each 100 μl to the 96-well plate. The optical absorption was measured using the plate-reader.

[0019] Results of the enhancing effect for differentiation -induction from human monocyte to macrophage measured by the above assay method are shown in Table 1.

Table 1

Structure of EM703 analogous derivatives and activities in THP-1/Mϕ system

Others		Treated conc. (μM)					ED_{50} (μM)*
EM	R_1	R_2	0.3	1	3	10	30	

703	Me	H		+	+	+	+	/	0.3
721	H	H		NT	NT	−	+	/	10
722	Et	H		−	+	+	++	/	1
723	Et	Et		−	+	+		/	1
724	Allyl	H		−	+	+	++	/	1
725	Allyl	Allyl		NT	−	±	+	/	3
726	Ac	H		−	−	−	−	−	−
727	Ms	Me		−	+	+	+	/	1
728	$CH_2C\equiv CH$	H		−	+	+	+	+	1
729	$CH_2C\equiv CH$	$CH_2C\equiv CH$		−	±	±	±	/	1
730	Pr	H		+	+	+	/	/	0.3
731	Pr	Pr		−	−	+	/	/	3
732	Bn	H		+	+	+	+	/	0.3
733	Bn	Bn		−	±	±	/	/	1
734				−	±	+	+	/	1
735				−	±	+	++	/	1
736	i-Pr	H		−	±	+	++	/	1
737	Me	Me	decladinose	NT	NT	−	+	/	10
738	C_6H_{13}	H		−	±	+	/	/	1
739	C_6H_{13}	C_6H_{13}		−	±	+	+	/	1
740	C_2H_4F	Me		±	±	+	+	+	0.3
742	CH_2CN	Me		−	−	−	+	+	10
743	Me	Me	Cl2oxime	NT	−	±	−	/	−
744	C_3H_6OH	Me		NT	−	−	−	/	−
745	C_2H_4OAc	Me		−	−	++	++	++	3

746	Me	Me C12MeCHOH	−	±	+	+	+	1
747			NT	NT	−	±	++	10
748			−	±	++	++	／	1
749	$(CH_2)_{10}Br$	$(CH_2)_{10}Br$	NT	±	+	+	/insolule	1
750	Me	Me C12MeCHNH$_2$	NT	−	−	±	／	10
751	H	Me C12MeCHOH	±	±	+	+	／	0.3
754	Me	H decladinose	NT	−	−	NT	+	30
EM	Me	MI	NT	−	±	+	+	3
CAM	Me	MI	NT	NT	−	+	−	10
EM oxim								
	Me	Me C9oxime	NT	−	±	±	++	3

[0020] In Table 1: Me: methyl; Pr : propyl; Et: ethyl; Ac: acetyl; and Ms: methanesulfonyl. *ED_{50}: Drug concentration (μM) required for 50% differentiation-induction of THP in Mϕ.

[0021] In Table 1, indicated activity is represented in comparison with enhancing action for differentiation-induction of EM 100 μM, and symbols are: ++: enhanced 100% or more; +: enhanced 50-100%; ± : enhanced 25-50%; -: no activity; /: expressed cytotoxicity; and NT: not tested or under assessment.

[0022] As shown in Table 1, since the smaller the value of ED_{50} (μ M) (minimum drug concentration required for 50% differentiation-induction from THP-1 to Mϕ), the stronger the differentiation-induction activity, it was found that the compounds of the present invention have enhancing action for differentiation-induction from THP-1 to Mϕ.

[0023] Next, the suppressive effect of the compound of the present invention (EM703) against bleomycin-induced pulmonary fibrosis was examined (hereinafter sometimes designates bleomycin as BLM).

[0024] A sample suspended in 5% gum arabic was orally administered, 50mg/kg/day for 17 days (from day-3 to day-13), and bleomycin, 100mg/kg, was administered from tail vein in day-0. On day-28, animals were sacrificed under anesthesia and fibrosis of the lungs was compared with non-administered mice. Suppressive effects are shown in Table 2.

References:

[0025] AzumaA., FurutaT., EnomotoT., HashimotoY., UematsuK., Nukariya N., Murata A., Kudoh S., Preventive effect of erythromycin on experimental bleomycin-induced acute lung injury in rats Thorax 53, 186-189, 1998

Table two

[Administration schedule]

BLM 100 mg/kg

↓

Day -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 28

EM703 50mg/kg/day ↓

sacrificed

Results: Hydroxyproline levels in tissue

Group		Assay result (μmol/l)	Weight conversion (μmol/g)
Cont		440	4.0
BLM	1	785	7.1
BLM	2	733	6.4
EM703	1	552	5.0
EM703	2	489	4.6
EM703	3	591	5.4
BLM+EM703	1	583	5.2
BLM+EM703	2	495	4.5
BLM+EM703	3	437	4.4
BLM+EM703	4	314	2.9
BLM+EM703	5		

Group:

[0026]

Cont (control) group (n=1)
BLM (bleomycin) group (n=2)
EM (erythromycin) group (n=4)
BLM (bleomycin) + EM (erythromycin) 703 group (n=5)

[0027] As indicated above, hydroxyproline is an index of lung fibrosis and higher value indicates hyperfibrosis. Hydroxyproline level, an index for lung injury, in BLM administered group was reduced in a group of BLM+EM703.

[0028] Next, the suppressive effect of the compound EM703 against pneumonia caused by influenza viral infection was examined.

[0029] Sample was dissolved in physiological saline containing 1% DMSO and amount corresponding to oral dosage of the small administration for long-term therapy was administered from day-1 to day-6 of the infection to mice influenza pneumonia model (0.3 mg and 0.03mg/mice), once a day, intraperitoneally. Results were compared with control group which was given only solvent.

Reference:

[0030] Sato K., Suga M., Akaike T. et al., Therapeutic effect of erythromycin on influenza virus-induced lung injury in mice. Am. J. Respir Crit. Care Med. 157, 853-859, 1998.

[0031] Results are shown in Fig.2 and Fig.3. In this system, mice developed pneumonia and almost died about 20 days after infection. Contrary to that, as shown in Fig. 2, administration of EM703, 0.3 mg/mice, cured pneumonia and 40% of mice were survived. Further, as shown in Fig. 3, mice without administration of drugs (control) indicated significant decrease of body weight due to pneumonia, but administration of EM703 indicated to increase body weight

from day-10. This indicates suppressive effect against pneumonia and result to cure pneumonia.

[0032] As described above, the compound of the present invention shows suppressive effect against influenza virus-induced pneumonia.

BRIEF DESCRIPTION OF THE FIGURES

[0033]

Fig. 1 shows an example of the synthetic scheme of the compound of the present invention.
Fig. 2 is a graph of the suppressive effect against pneumonia showing relationship between numbers of day after infection due to influenza virus infection and survival rates of the compound of the present invention.
Fig. 3 is a graph showing suppressive effect of the compound of the present invention on bleomycin-induced pulmonary fibrosis.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0034] The present invention is explained by illustrating referential examples and examples, but is not limited within these examples.

REFERENTIAL EXAMPLE 1

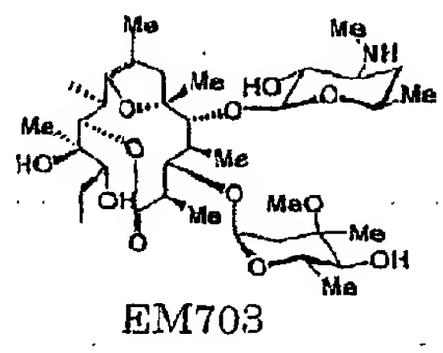
Synthesis of EM701

[0035] Glacial acetic acid solution of erythromycin A (12.4 g, 16.9 mmol) was stirred at room temperature for 2 hours, added slowly aqueous sodium hydrogen carbonate and neutralized. The reaction mixture was extracted with chloroform, dehydrated the organic layer with sodium sulfate, filtered off the sodium sulfate and removed the solvent by distillation to obtain crude substance. The crude substance was purified with silica gel chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM201 (7.7 g, 63%). Subsequently, potassium carbonate (1.4 g, 10.6 mmol) was added to the methanol solution (100ml) of EM 201 (7.6 g, 10.6 mmol) and refluxed for 2 hours. After distilled off the solvent, the residue was dissolved in aqueous sodium hydrogen carbonate and extracted with chloroform. The mixture was dehydrated with sodium sulfate, filtered and removed the sodium sulfate, then the obtained crude substance was purified by silica gel chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM701 (5.9g, 78%, white powder).

EXAMPLE 1

Synthesis of de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM703)

[0036]



EM703

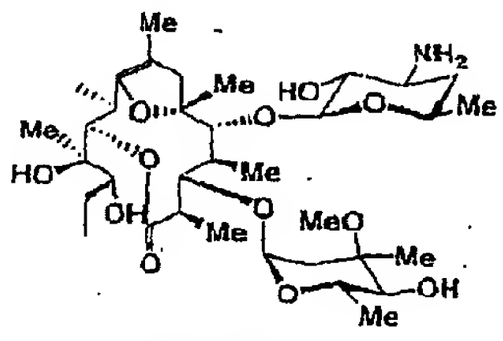
[0037] Sodium acetate (3.9 g, 48.5 mmol) and iodine (2.5 g, 9.7 mmol) were added in this order to methanol (52.0 mL)-water (13.0 mL) solution of EM701 (6.9 g, 9.7 mmol) at room temperature, and stirred at 50°C for 3 hours. During the stirring, 1N aqueous solution of sodium hydroxide was added to maintain at pH 8-9 continuously. After confirming the completion of the reaction by TLC, the reaction mixture was diluted with aqueous ammonia (7.5 mL)-water (200 mL), and extracted with dichloromethane. After dehydrating the organic layer with sodium sulfate, the sodium sulfate was removed by filtration and distilled off the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 0.01 → 10 : 1 : 0.05) to obtain

EM703 (4.8 g, Yield: 70%, white powder).
EM703: m. p. : 177-180°C.

EXAMPLE 2

Synthesis of bis-de(3'-N-methyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM721)

[0038]



EM721

[0039] Sodium (4.5 g, 1.67 mmol) was added in methanol (15 mL) to prepare methanol solution of sodium methoxide, and EM703 (195.4 mg, 0.279 mmol) and iodine (353.6 mg, 1.393 mmol) were added in this order at 0°C and stirred for 3 hours. After confirming completion of the reaction by TLC, sodium thiosulfate (0.8 g), aqueous ammonia (0.5 mL) and water (80 mL) were added and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM721 (166.3 mg, Yield: 87%, white powder).

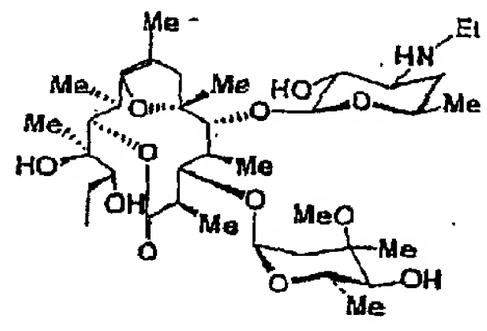
EM721 : m. p. : 134-136°C.
IR (KBr) υ : 3467.4, 2973.7, 2935.1, 2879.2, 1700.9, 1637.3, 1457.9, 1380.8, 1265.1, 1166.7, 1126.2, 1079.9, 1037.5, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{35}H_{61}NO_{12}Na$ [M+Na] +	
Calculated	710.4091,
Found	710.4060.

EXAMPLE 3

Synthesis of bis-de(3'-N-methyl)-3'-N-ethyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM722)

[0040]



EM722

[0041] N,N-Diisopropylethylamine (26.6 μL, 0.153 mmol) and ethyl iodide (12.2 μL, 0.153 mmol) were added to dimethylformamide (1.0 mL) solution of EM721 (21.0mg. 0.0305 mmol) and stirred at room temperature for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with

dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM722 (7.0 mg, Yield: 32%, white powder).

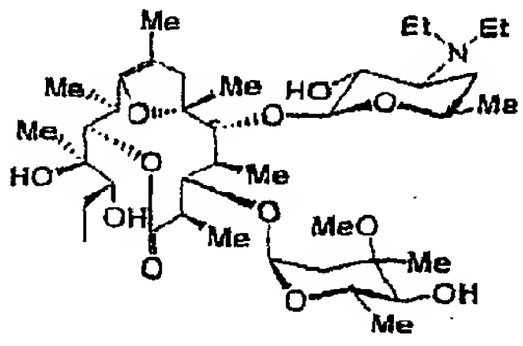
EM722 : m. p. : 124-126°C.
IR (KBr) υ : 3471.6, 2933.2, 1704.8, 1457.9, 1378.9, 1263.1, 1166.7, 1128.2, 1074,2, 1037.5, 1018.2 cm^{-1}.

HRMS (FAB)m/z : $C_{37}H_{65}NO_{12}Na$ $[M+Na]^+$	
Calculated	738.4404
Found	738.4393.

EXAMPLE 4

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-diethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM723)

[0042]



EM723

[0043] N,N-Diisopropylethylamine (26.6 μL, 0.153 mmol) and ethyl iodide (12.2 μL, 0.153 mmol) were added to dimethylformamide (1.0 mL) solution of EM721 (21.0 mg, 0.0305 mmol) and stirred at room temperature for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM723 (10.3 mg, Yield: 45%, white powder).

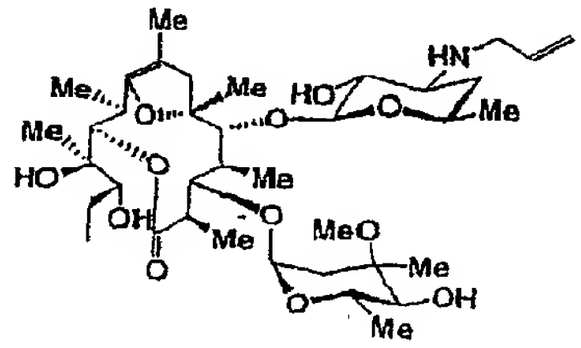
EM723 : m. p. : 165-168°C.
IR (KBr) υ : 3473.7, 2935.1, 1699.0, 1382.7, 1317.1, 1267.0, 1166.7, 1126.2, 1108,9, 1078.0, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{39}H_{69}NO_{12}Na$ $[M+Na]^+$	
Calculated	736.4717
Found	766.4710.

EXAMPLE 5

Synthesis of bis-de(3'-N-methyl)-3'-N-allyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM724)

[0044]



EM724

[0045] Allyl bromide (148.3 μL, 1.714 mmol) was added to dichloromethane (5.7 mL) solution of EM721 (117.8 mg, 0.171 mmol) and N,N-Diisopropylethylamine (298.6 μL, 1.714 mmol) at 0°C and stirred at room temperature for 2 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM724 (21.9 mg, Yield: 30%, white powder) was obtained.

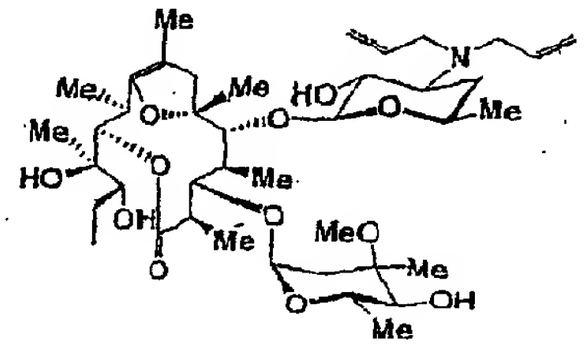
EM724 : m. p. : 106-109°C.
IR (KBr) υ : 3448.8, 2971.8, 2933.2, 1718.3, 1637.3, 1380.8, 1265.1, 1166.7, 1126,2, 1078.0, 1037.5, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{65}NO_{12}Na$ $[M+Na]^+$	
Calculated	750.4404,
Found	750.4420.

EXAMPLE 6

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-diallyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM725)

[0046]



EM725

[0047] Allyl bromide (148.3 μL, 1.714 mmol) was added to dichloromethane (5.7 mL) solution of EM721 (117.8 mg, 0.171 mmol) and N,N-Diisopropylethylamine (298.6μL, 1.714 mmol) at 0°C, stirred at room temperature for 2 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate,

and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM725 (64.3 mg, Yield: 59%, white powder).

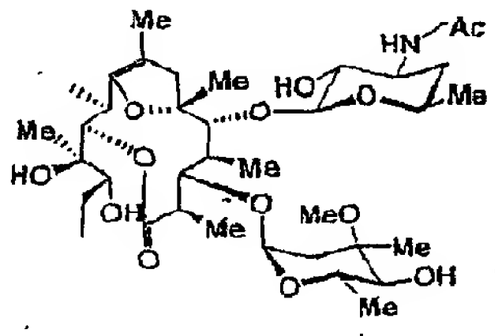
EM725 : m. p. : 140-142 °C.
IR (KBr) υ : 3471.7, 2971.8, 2927.4, 1700.9, 1637.3, 1380.8, 1317.1, 1265.1, 1166.7, 1124.3, 1114.7, 1049.1, 1016.3cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{69}NO_{12}Na$ $[M+Na]^+$	
Calculated	790.4717
Found	790.4716.

EXAMPLE 7

Synthesis of bis-de(3'-N-methyl)-3'-N-acetyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM726)

[0048]



EM726

[0049] Acetic anhydride (8.4 μL, 0.0759 mmol) was added to dichloromethane (1.6 mL) solution of EM721 (34.8 mg, 0.0506 mmol) at 0°C, stirred for 10 minutes and further stirred at room temperature for 30 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, anad removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol = 100 : 1 → 20 : 1) to obtain EM726 (33.4 mg, Yield: 91%, white powder).

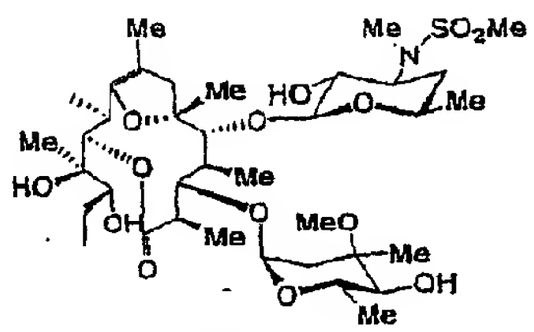
EM726 : m. p. : 137-139 °C.
IR (KBr) υ : 3417.2, 2973.7, 2935.1, 1699.0, 1454.1, 1376.9, 1317.1, 1268.9, 1166,7, 1124.3, 1076.1, 1033.7, 1018.2, 1000.9 cm^{-1}.

HRMS (FAB)m/z : $C_{37}H_{63}NO_{13}Na$ $[M+Na]^+$	
Calculated	752.4197
Found	752.4202.

EXAMPLE 8

Synthesis of de(3'-N-methyl)-3'-N-sulfonyl-8,9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM727)

[0050]



EM727

[0051] Methanesulfonyl chloride (9.3μL, 0.249 mmol) was added to dichloromethane (4.2 ml) solution of EM703 (87.6 mg, 0.125 mmol) at 0°C and stirred for 3 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol = 100 : 1 → 20 : 1) to obtain EM727 (37.2 mg, Yield: 91%, white powder).

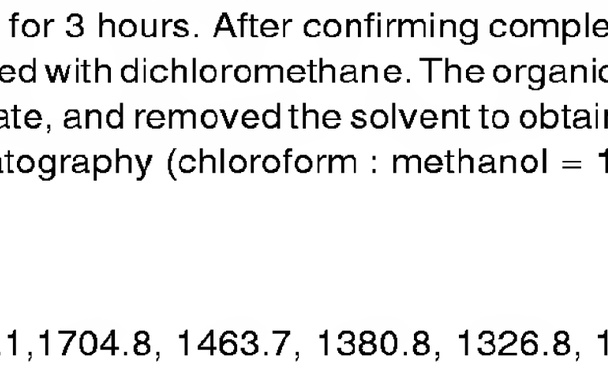
EM727 : m. p. ; 225-228 °C.
IR (KBr) υ : 3497.6, 2973.7, 2935.1,1704.8, 1463.7, 1380.8, 1326.8, 1319.1, 1265,1, 1166.7, 1141.7, 1074.2, 1041.4, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{37}H_{65}NO_{14}SNa$ $[M+Na]^+$	
Calculated	802.4023
Found	802.3995.

EXAMPLE 9

Synthesis of bis-de(3'-N-methyl)-3'-N-propargyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM728)

[0052]



EM728

[0053] 3-Bromopropine (137.8 μL, 1.546 mmol) was added to dichloromethane (5.2 mL) solution of EM721 (106.3 mg, 0.155 mmol) and N,N-Diisopropylethylamine (269.3 μL, 1.546 mmol), and stirred at room temperature for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1: 0.05) to obtain EM728 (41.3 mg, Yield: 37%, white powder).

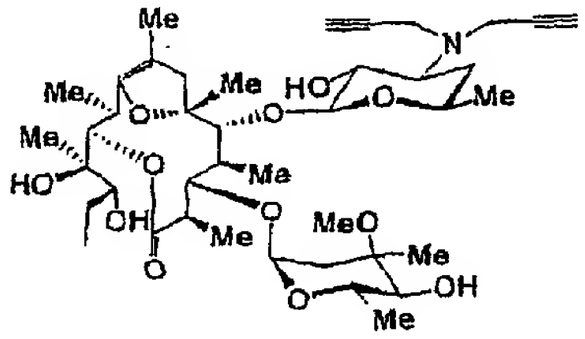
EM728 : m. p. : 113-115 °C.
IR (KBr) υ : 3413.0, 2973.7, 2935.1, 1706.8, 1457.9, 1382.7, 1263.1, 1166.7, 1126,2, 1078.0, 1039.4, 1016.5 cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{63}NO_{12}Na$ $[M+Na]^+$	
Calculated	748.4248
Found	748.4260.

EXAMPLE 10

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-propargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM729)

[0054]



EM729

[0055] 3-Bromopropine (137.8 μL, 1.546 mmol) was added to dichloromethane (5.2 mL) solution of EM721 (106.3 mg, 0.155 mmol) and N,N-Diisopropylethylamine (269.3 μL, 1.546 mmol) and stirred at room temperature for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1: 0.05) to obtain EM729 (27.9 mg, Yield: 24%, white powder).

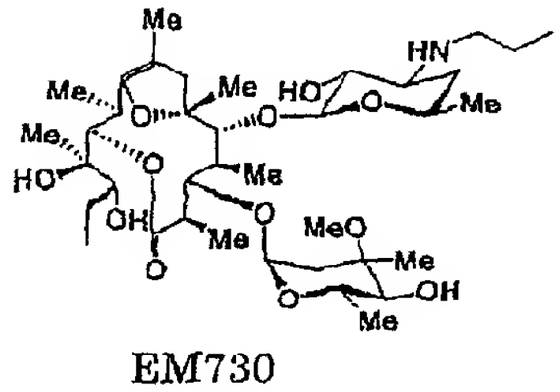
EM729 : m. p. : 123-125 °C.
IR (KBr) υ : 3415.0, 3309.2, 2971.8, 2933.2, 2877.3, 1706.7, 1457.9, 1375.0, 1263.1, 1166.7, 1116.6, 1072.2, 1049.1, 1035.6, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{65}NO_{12}Na$ $[M+Na]^+$	
Calculated	786.4404
Found	786.4404.

EXAMPLE 11

Synthesis of bis-de(3'-N-methyl)-3'-N-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM730)

[0056]



EM730

[0057] N,N-Diisoproplylethylamine (59.6 μL, 0.342 mmol) and 1-iodopropane (33.3μL, 0.342 mmol) were added in this order to acetinitrile (2.3 mL) solution of EM721 (23.5 mg, 0.0342 mmol) and refluxed at 80°C for 20 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM730 (5.7 mg, Yield: 23%, white powder).

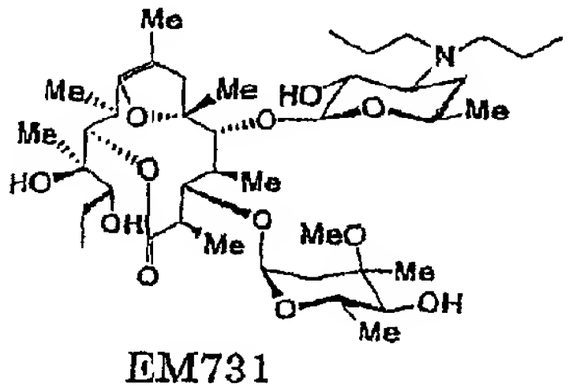
EM730 : m. p. : 109-111 °C.
IR (KBr) υ : 3435.0, 2971.8, 2935.1, 2879.2, 1706.7, 1459.8, 1380.8, 1263.1, 1166.7, 1126.2, 1078.0, 1035.6, 1016.3cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{67}NO_{12}Na$ $[M+Na]^+$	
Calculated	752.4560
Found	752.4564.

EXAMPLE 12

Synthesis of bis-de(3'-N-methyl)-3',3'-N, N-di-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM731)

[0058]



EM731

[0059] N,N-Diisopropylethylamine (59.6 μL, 0.342 mmol) and 1-iodopropane (33.3μL, 0.342 mmol) were added in this order to acetinitrile (2.3 mL) solution of EM721 (23.5 mg, 0.0342 mmol) and refluxed at 80°C for 20 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography

(chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM731 (12.0 mg, Yield: 40%, white powder).

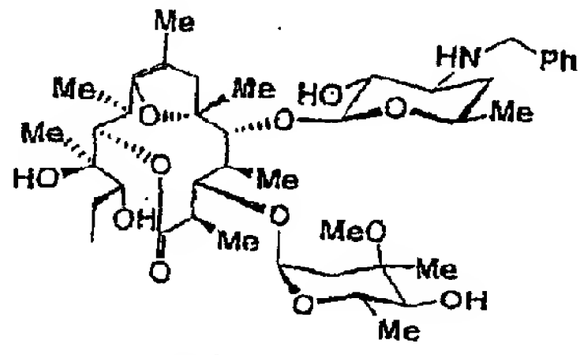
EM731 : m. p. : 148-151 °C.
IR (KBr) υ : 3435.0, 2964.1, 2933.2, 2873.4, 1706.7, 1457.9, 1376.9, 1319.1, 1263.1, 1166.7, 1110.8, 1081.9, 1049.1, 1035.6, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{73}NO_{12}Na$ $[M+Na]^+$	
Calculated	794.5030
Found	794.5005

EXAMPLE 13

Synthesis of bis-de(3'-N-methyl)-3'-N-benzyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM732)

[0060]



EM732

[0061] Benzyl chloride (297.3 μL, 2.584 mmol) was added to dichloromethane (4.3 mL) solution of EM721 (88.8 mg, 0.129 mmol) and N,N-diisopropylethylamine (450.1 μL, 2.584 mmol) at room temperature and stirred for 96 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM732 (49.9 mg, Yield: 50%, white powder).

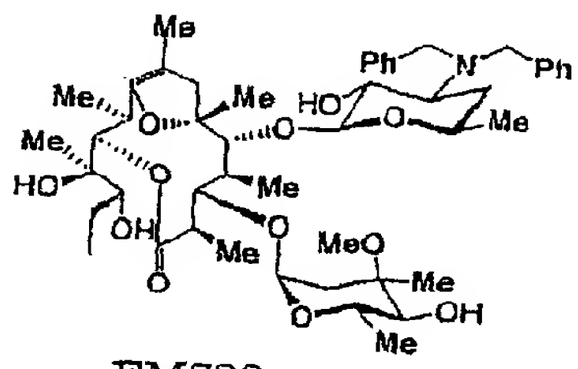
EM732 : m. p. 126-128 °C.
IR (KBr) υ : 3410.0, 2971.8, 2935.1, 1706.7, 1456.0, 1378.9, 1263.1, 1166.7, 1124.3, 1078.0, 1049.1, 1039.4, 1016.3, 983.5, 937.2, 808.0, 752.1 cm^{-1}.

HRMS (FAB)m/z : $C_{42}H_{67}NO_{12}Na$ $[M+Na]^+$	
Calculated	800.4560
Found	800.4565

EXAMPLE 14

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-benzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM733)

[0062]



EM733

[0063] N,N-Diisopropylethylamine (135.9μL, 0.780 mmol) and benzyl chloride (89.7μL, 0.780 mmol) were added in this order to acetinitrile (1.3 mL) solution of EM721 (26.8 mg, 0.0390 mmol) and refluxed at 80°C for 60 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM733 (19.6 mg, Yield: 58%, white powder).

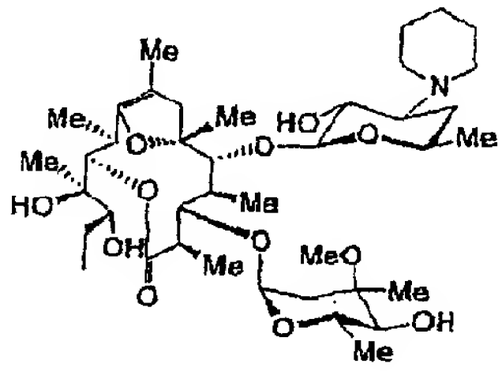
EM733 : m. p. : 149-152 °C.
IR (KBr) υ : 3420.6, 2969.8, 2935.1, 1700.9, 1454.1, 1375.0, 1324.9, 1263.1, 1166.7, 1116.6, 1076.1, 1049.1, 1016.3, 752.1, 700.0 cm^{-1}

HRMS (FAB)m/z : $C_{49}H_{73}NO_{12}Na$ $[M+Na]^+$	
Calculated	890.5030
Found	890.5032

EXAMPLE 15

Synthesis of de(3'-dimethylamino)-3'-piperidino-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM734)

[0064]



EM734

[0065] N,N-Diisopropylethylamine (42.5 μL, 0.244 mmol) and 1,5-dibromopentane (33.2μL, 0.244 mmol) were added in this order to acetinitrile (4.9 mL) solution of EM721 (16.8 mg, 0.0244 mmol) and refluxed at 80°C for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM734 (13.3 mg, Yield: 72%, white powder).

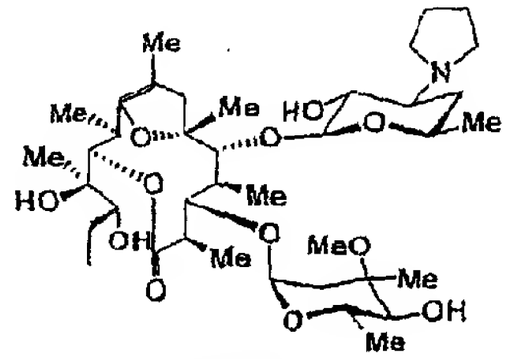
EM734 : m. p. : 128-130 °C.
IR (KBr) υ : 3420.0, 2971.8, 2935.1, 2858.0, 1710.6, 1454.1, 1380.8, 1319.1, 1263.1, 1164.8, 1110.8, 1074.2, 1047.2, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{40}H_{70}NO_{12}$ $[M+Na]^+$	
Calculated	756.4897
Found	756.4901

EXAMPLE 16

Synthesis of de(3'-dimethylamino)-3'-pyrrolidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM735)

[0066]



EM735

[0067] N,N-diisopropylethylamine (40.2 μL, 0.231 mmol) and 1,4-dibromobutane (27.6μL, 0.231 mmol) were added in this order to acetinitrile (4.6 mL) solution of EM721 (15.9 mg, 0.0231 mmol) and refluxed at 80°C for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM735 (11.9 mg, Yield: 70%, white powder).

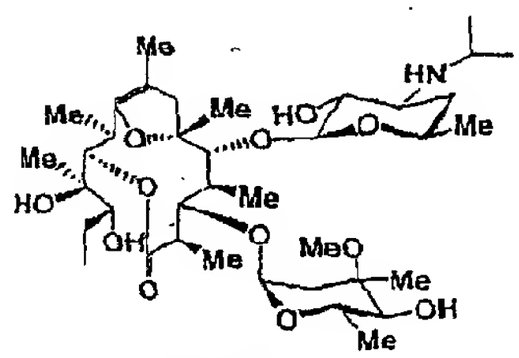
EM735 : m. p. : 127-129 °C.
IR (KBr) υ : 3420.0, 2971.8, 2937.1, 1702.8, 1457.9, 1382.7, 1265.1 1166.7, 1124.3, 10761.1, 1049.1, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{39}H_{68}NO_{12}[M+Na]^+$	
Calculated	742.4741
Found	742.4743

EXAMPLE 17

Synthesis of bis-de(3'-N-methyl)-3'-N-(2-propyl)-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM736)

[0068]



EM736

[0069] N,N-Diisopropylethylamine (459.2 μL, 2.636 mmol) and 2-bromopropane (247.5μL, 2.636 mmol) were added in this order to acetinitrile (4.4 mL) solution of EM721 (90.6 mg, 0.132 mmol) and stirred at 80°C for 72 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM736 (25.3 mg, Yield: 26%, white powder). The raw material EM721 was recovered 47.1 mg (Yield: 52%).

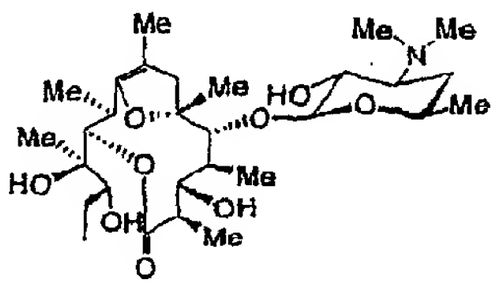
EM736 : m. p. : 102-104 °C.
IR (KBr) υ : 3420.0, 2971.8, 2933.2, 2877.3, 1718.3, 1459.8, 1380.8, 1263.1, 1166.7, 1126.2, 1078.0, 1049.1, 1016.3cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{67}NO_{12}Na$ $[M+Na]^+$	
Calculated	752.4560
Found	752.4576.

EXAMPLE 18

Synthesis of de(3-O-cladinosyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM737)

[0070]



EM737

[0071] p-toluenesulfonic acid monohydrate (80.3μL, 0.422 mmol) was added to dimethylformamide (5.6 mL) solution of EM701 (201.6 mg, 0.282 mmol) and stirred at 50°C for 8 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water, adjusted to pH 8.0 by adding saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove

the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM737 (84.7 mg, Yield: 54%, white powder).

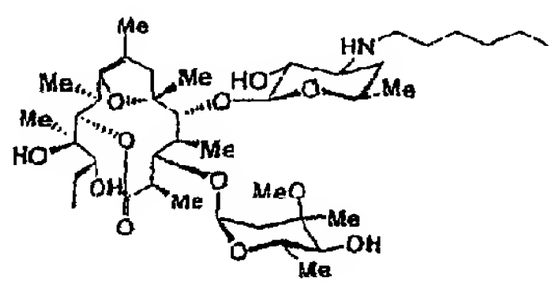
EM737 : m. p. : 109-111 °C.
IR (KBr) υ : 3486.7, 2973.7, 2937.1, 2877.3, 1708.6, 1631.5, 1457.9, 1382.7, 1265.1, 1164.8, 1110.8, 1076.1, 1039.4 cm^{-1}.

HRMS (FAB)m/z : $C_{29}H_{52}NO_9$ $[M+Na]^+$	
Calculated	558.3641
Found	558.3616

EXAMPLE 19

Synthesis of bis-de(3'-N-methyl)-3'-N-hexyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM738)

[0072]



EM738

[0073] N,N-Diisopropylethylamine (408.5 μL, 2.345 mmol) and 1-bromohexane (328.7μL, 2.345 mmol) were added in this order to acetinitrile (3.9 mL) solution of EM721 (80.6 mg, 0.117 mmol) and stirred at 60°C for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM738 (33.7 mg, Yield: 45%, white powder). The raw material EM721 was recovered 24.6 mg (Yield: 31%).

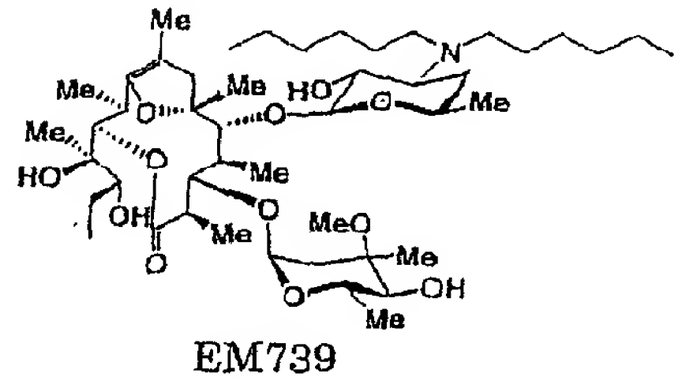
EM738 : m. p. : 115-118 °C.
IR (KBr) υ : 3430.3, 2969.8, 2933.2, 2858.0, 1712.5, 1459.8, 1378.9, 1317.1, 1263.1, 1166.7, 1126.2, 1078.0, 1047.2, 1039.4, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{74}NO_{12}$ $[M+Na]^+$	
Calculated	772.5210
Found	772.5214.

EXAMPLE 20

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-dihexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM739)

[0074]



EM739

[0075] N,N-Diisopropylethylamine (116.0μL, 0.666 mmol) and 1-bromohexane (93.6μL, 0.666 mmol) were added in this order to acetinitrile (1,1 mL) solution of EM721 (22.9 mg, 0.0333 mmol) and stirred at 60°C for 72 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM739 (20.1 mg, Yield: 71%, white powder).

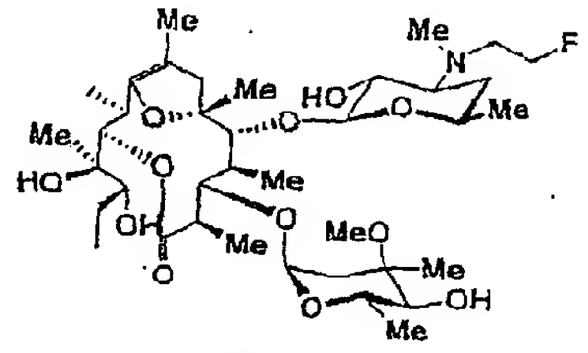
EM739 : m. p. : 158-160 °C.
IR (KBr) υ : 3490.0, 2958.3, 2931.3, 2871.5, 2858.0, 1702.8, 1459.8, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1083.8, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{47}H_{86}NO_{12}$ $[M+H]^+$	
Calculated	856.6149
Found	856.6132.

EXAMPLE 21

Synthesis of bis-de(3'-N-methyl)-3'-N-(2-fluoroethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM740)

[0076]



EM740

[0077] N,N-Diisopropylethylamine (347.7 μL, 1.996 mmol) and 1-bromo-2-fluoroethane (148.6μL, 1.996 mmol) were added to dimethylformamide (3.3 mL) solution of EM703 (70.0 mg, 0.0998 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column

chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM740 (36.0 mg, Yield: 48%, white powder). The raw material EM703 was recovered 25.5 mg (Yield: 36%).

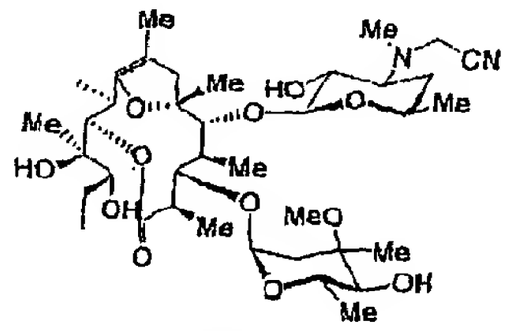
EM740 : m. p. : 138-140 °C.
IR (KBr) υ : 3480.8, 2973.7, 2937.1, 2879.2, 1704.8, 1457.9, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1114.7, 1076.1, 1049.1, 1035.6, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{66}NO_{12}Fna$ $[M+Na]^+$	
Calculated	770.4467
Found	770.4469.

EXAMPLE 22

Synthesis of de(3'-N-methyl)-3'-cyanomethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM742)

[0078]



EM742

[0079] N,N-Diisopropylethylamine (320.9 μL, 1.847 mmol) and bromoacetinitrile (128.3 μL, 1.847 mmol) were added to dimethylformamide(3.1 mL) solution of EM703 (64.6 mg, 0.0921 mmol) at room temperature and stirred for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM742 (53.1 mg, Yield: 78%, white powder).

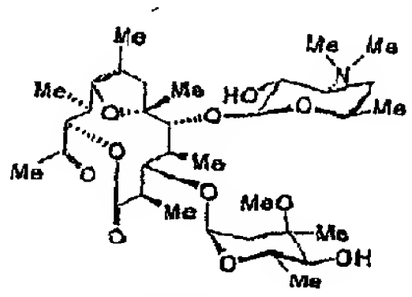
EM742 : m. p. : 110-112 °C.
IR (KBr) υ : 3485.5, 2973.7, 2935.1, 2863.8, 1702.8, 1456.0, 1382.7, 1319.1, 1265.1, 1166.7, 1126.2, 1074.2, 1037.5, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{64}N_2O_{12}Na$ $[M+Na]^+$	
Calculated	763.4356
Found	763.4377.

REFERENTIAL EXAMPLE 2

Synthesis of de(12-hydroxy)-de[12-(1-hydroxypropyl)]-12 -oxo-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM705)

[0080]



EM705

[0081] Lead tetraacetate (508.0 mg, 1.136 mmol) was added to dichloromethane (24.0 ml) solution of EM701 (508.0 mg, 0.701 mmol) and stirred at room temperature for 40 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01) to obtain EM705 (282.7 mg, Yield: 61%, white powder).

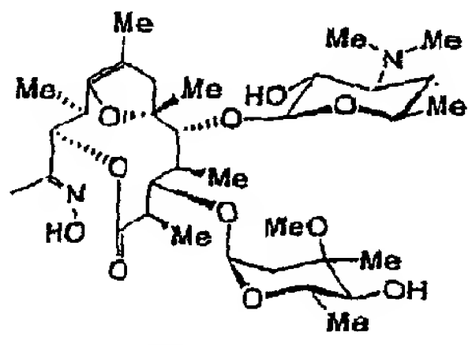
EM705 : m. p. : 108-112 °C.
IR (KBr) υ : 3488, 2972, 2883, 1740, 1724, 1458, 1379, 1244, 1165, 1107, 1093, 1076, 1055, 1034, 1016 cm^{-1}.

HRMS (FAB) : $C_{34}H_{58}NO_{11}$ $[M+H]^+$	
Calculated	656.4010
Found	656.4021.

EXAMPLE 23

Synthesis of de(12-hydroxy)-de[12-(1-hydroxypropyl)]-12 -hydroxyoxime- 8,9-anhydro-pseudoerythromycin A 6,9-hemiketal (EM743) and the salt thereof

[0082]



EM743

[0083] Pyridine (0.9 mL) was slowly added at 0°C to ethanol (0.9 mL) solution of EM705 (116.5 mg, 0.1781 mmol) and hydroxylamine hydrochloride (32.0 mg, 0.533 mmol) and stirred for 3 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extractedwith dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain

crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM743 (114.5 mg, Yield: 96%, white powder).

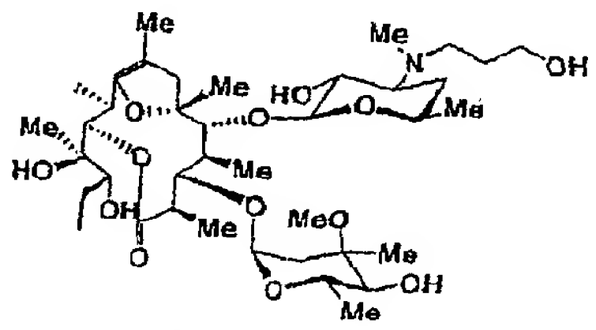
EM743 : m. p. : 141-143 °C.
IR (KBr) υ : 3485.8, 2971.8, 2937.1, 2883.1, 1737.5, 1459.8, 1378.9, 1255.4, 1247.7, 1166.7, 1112.7, 1089.6, 1076.1, 1037.5, 1014.4 cm^{-1}.

HRMS (FAB)m/z : $C_{34}H_{59}N_2O_{11}[M+H]^+$	
Calculated	671.4112
Found	671.4108.

EXAMPLE 24

Synthesis of de[(3'-N-methyl)-[3'-N-(3-hydroxy-1-propyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM744)

[0084]



EM744

[0085] N,N-Diisopropylethylamine (338.3 μL, 1.942 mmol) and 3-bromo-1-propanol (175.6 μL, 1.942 mmol) were added to dimethylformamide (3.3 mL) solution of EM703 (68.1 mg, 0.0971 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM744 (27.7 mg, Yield: 38%, white powder). The raw material EM703 was recovered 22.5 mg (Yield: 33%).

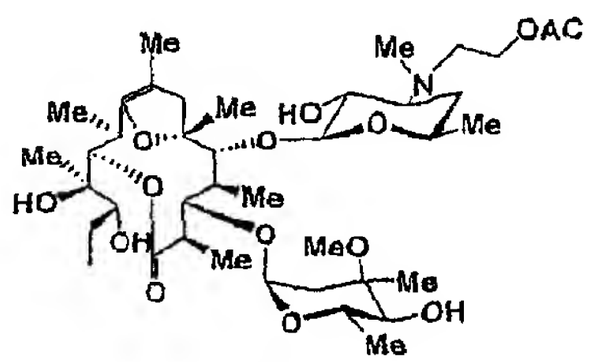
EM744 : m. p. : 142-145 °C.
IR (KBr) υ : 3478.8, 2973.7, 2937.1, 2877.3, 1700.9, 1635.3, 1459.8, 1403.9, 1382.7, 1317.1, 1267.0, 1166.7, 1126.2, 1114.7, 1076.1, 1049.1, 1035.6, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{39}H_{69}NO_{13}Na$ $[M+Na]^+$	
Calculated	782.4666
Found	782.4667.

EXAMPLE 25

Synthesis of de(3'-N-methyl)-3'-N-(2-acetoxyethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM745)

[0086]



EM745

[0087] N,N-Diisopropylethylamine (106.8 μL, 0.613 mmol) and 2-bromoethylacetate (67.6 μL, 0.613 mmol) were added to dimethylformamide (1.0 mL) solution of EM703 (21.5 mg, 0.0307 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM745 (6.0 mg, Yield: 25%, white powder).

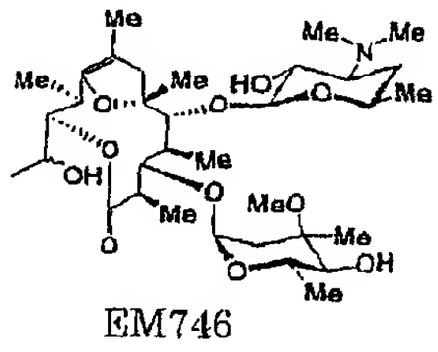
EM745 : m. p. : 131-133 °C.
IR (KBr) υ : 3500.2, 3477.0, 2973.7, 2937.1, 2877.3, 1735.6, 1700.9, 1457.9, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1078.0, 1037.5, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{40}H_{69}NO_{14}Na$ $[M+Na]^+$	
Calculated	810.4615
Found	810.4629

EXAMPLE 26

Synthesis of de[12-(hydroxypropyl)]-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM746)

[0088]



EM746

[0089] Sodium borohydride (21.8 mg, 0,575 mmol) was added to methanol (2.9 mL) solution of EM705 (37.7 mg, 0.0575 mmol) at -78°C and stirred for 30 minutes. Temperature of the reaction mixture was increased to 0°C and further stirred for 30 minutes. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 ml). The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol :

aqueous ammonia = 15 : 1 : 0.1) to obtain EM746 (35.8 mg, Yield: 95%, white powder).

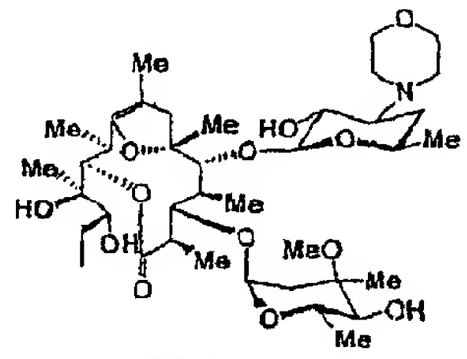
EM746 : m. p. : 116-118 °C.
IR (KBr) υ : 3457.7, 2971.3, 2939.0, 1731.8, 1631.5, 1457.9, 1378.9, 1265.1, 1166.7, 1110.8, 1078.0, 1041.4; 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{34}H_{59}NO_{11}Na$ $[M+Na]^+$	
Calculated	680.3963
Found	680.3963

EXAMPLE 27

Synthesis of de(3'-dimethylamino)-3'-morpholino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM747)

[0090]



EM747

[0091] N,N-Diisopropylethylamine (45.8 μL, 0,263 mmol) and bis(2-bromoethyl) ether (33.1 μL, 0.263 mmol) were added in this order to acetinitrile (2.6 mL) solution of EM721 (18.1 mg, 0.0263 mmol) and stirred at 80°C for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM747 (12.0 mg, Yield: 60%, white powder).

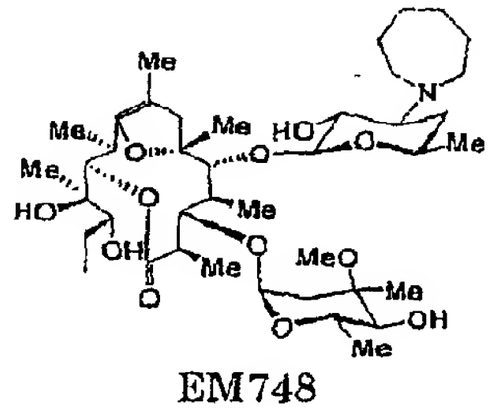
EM747 : m. p. : 139-142 °C.
IR (KBr) υ : 3452.0, 2971.8, 2937.1, 2865.7, 1700.9, 1646.9, 1457.9, 1380.8, 1319.1, 1265.1, 1166.7, 1110.8, 1072.2, 1049.1, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{39}H_{67}NO_{13}$ Na $[M+Na]^+$	
Calculated	780.4510
Found	780.4529

EXAMPLE 28

Synthesis of de(3'-dimethylamino)-3'-[hexahydro-1(1H) -azepinyl]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM748)

[0092]



EM748

[0093] N,N-Diisopropylethylamine (49.5 μL, 0,284 mmol) and 1,6-dibromohexane (43.6 μL, 0.284 mmol) were added in this order to acetinitrile (2.8 ml) solution of EM721 (19.5 mg, 0.0284 mmol) and stirred at 80°C for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM748 (11.7 mg, Yield: 54%, white powder).

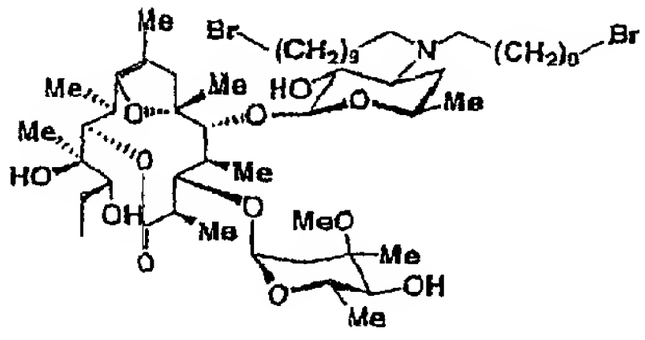
EM748 : m. p. : 120-123 °C.
IR (KBr) υ : 3430.7, 2971.8, 2933.2, 2858.0, 1708.6, 1629.6, 1457.9, 1378.9, 1319.1, 1263.1, 1166.7, 1112.7, 1083.8, 1047.2, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{72}NO_{12}[M+H]^+$	
Calculated	770.5054
Found	770.5062.

EXAMPLE 29

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-(10-bromo -1-decanyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM749)

[0094]



EM749

[0095] N,N-Diisopropylethylamine (45.6 μL, 0,262 mmol) and 1,10-dibromodecane (58.9 μL, 0.262 mmol) were added in this order to acetinitrile (2.6 mL) solution of EM721 (18.0 mg, 0.0262 mmol) and refluxed at 80°C for 36 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with

dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM749 (14.9 mg, Yield: 51%, white powder).

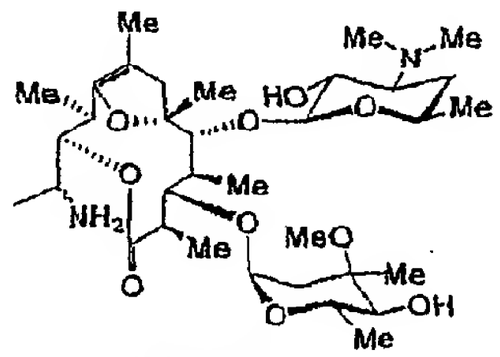
EM749 : m. p. : 132-134 °C.
IR (KBr) υ : 3448.1, 2929.3, 1700.9, 1629.6, 1459.8, 1375.0, 1319.1, 1267.0, 1166.7, 1126.2, 1081.9, 1049.1, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{55}H_{100}NO_{12}Br_2$ $[M+H]^+$	
Calculated	1126
Found	1126.

EXAMPLE 30

Synthesis of de(12-hydroxy)-de[12-(hydroxypropyl)]-12 -amino-8,9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM750)

[0096]



EM750

[0097] Molybdenum oxide (IV) (10.0 mg, 0,0694 mmol) and sodium borohydride (10.5 mg, 0.277 mmol) were added to ethanol (2.3 mL) solution of EM743 (15.5 mg, 0.0231 mmol) at 0°C and stirred for 4 hours. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 mL), and the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM750 (13.4 mg, Yield: 88%, white powder).

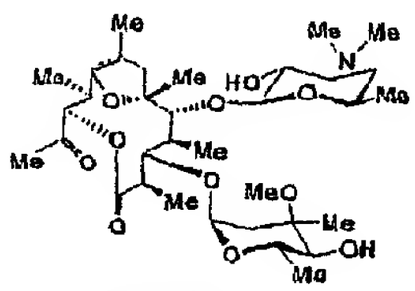
EM750 : m. p. : 104-107 °C.
IR (KBr) υ : 3448.1, 2971.8, 2935.1, 1729.8, 1629.6, 1457.9, 1378.9, 1259.3, 1166.7, 1114.7, 1078.0, 1039.4, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{34}H_{60}N_2O_{10}Na$ $[M+Na]^+$	
Calculated	679.4145
Found	679.4117.

REFERENTIAL EXAMPLE 3

Synthesis of de(3'-N-methyl)-de(12-hydroxy)-de-[12-(1-hydroxy propyl)]-12-oxo-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM706)

[0098]



EM706

[0099] Lead tetraacetate (508.0 mg, 1.136 mmol) was added to dichloromethane (24.0 ml) solution of EM701 (508.0 mg, 0.701 mmol) and stirred at room temperature for 40 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01) to obtain EM706 (71.6 mg, Yield: 16%, white powder).

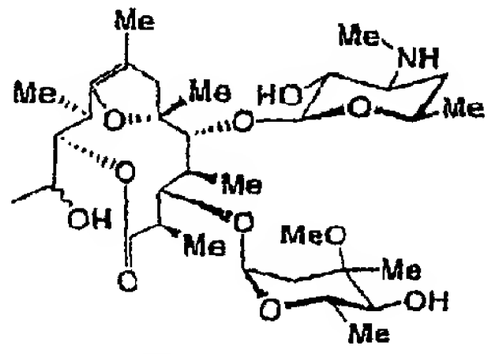
EM706 : m. p. : 176-179 °C.
IR (KBr) υ : 3468, 2966, 2852, 2360, 1736, 1718, 1558, 1462, 1379, 1246, 1165, 1126, 1099, 1076, 1038, 1016 cm^{-1}.

HRMS (FAB)m/z : $C_{33}H_{56}NO_{11}$ $[M+H]^+$	
Calculated	642.3853
Found	642.3866.

EXAMPLE 31

Synthesis of de(3'-N-methyl)-de[12-(1-hydroxypropyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM751)

[0100]



EM751

[0101] Sodium borohydride (22.9 mg, 0.605 mmol) was added to methanol (3.0 mL) solution of EM706 (38.8 mg, 0.0605 mmol) at 0°C and stirred for 1 hour. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 mL), and the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1)

to obtain EM751 (31.4 mg, Yield: 81%, white powder).

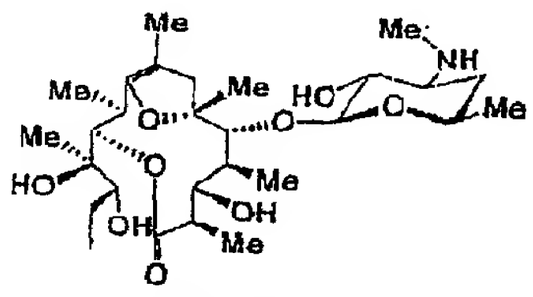
EM751 : m. p. : 123-125 °C.
IR (KBr) υ : 3504.0, 2448.1, 2971.8, 2935.1, 1729.8, 1664.3,1594.8, 1457.9, 1378.9, 1334.1, 1265.1, 1166.7, 1126.2, 1078.0, 1041.4, 1016 cm^{-1}.

HRMS (FAB)m/z : $C_{33}H_{58}NO_{11}[M+H]^+$	
Calculated	644.3987
Found	644.4011

EXAMPLE 32

Synthesis of de(3-O-cladinosyl)-de(3'-N-methyl)-8,9-anhydrous -pseudoerythromycin A 6, 9-hemiketal (EM754)

[0102]



EM754

[0103] p-toluenesulfonic acid monohydrate (53.9 mg, 0.283 mmol) was added to dimethylformamide (3.8 mL) solution of EM703 (132.4 mg, 0.189 mmol) and stirred at 50°C for 6 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water, adjusted to pH 8 by adding saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM754 (50.2 mg, Yield: 49%, white powder).

EM754 : m. p. : 218-221 °C.
IR (KBr) υ : 3432.7, 2969.8, 2927.4, 2858.0, 1708.6, 1629.6, 1457.9, 1405.9, 1380.8, 1319.1, 1270.9, 1232.3, 1130.1, 1078.0, 1039.4 cm^{-1}.

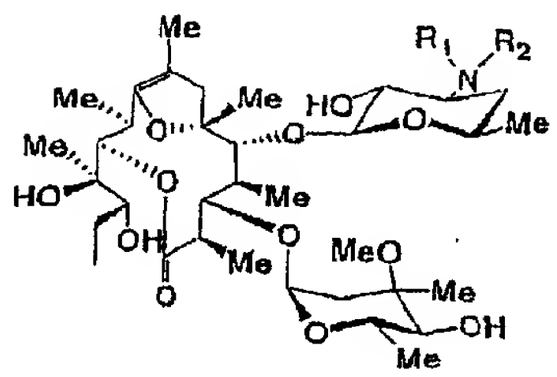
HRMS (FAB)m/z : $C_{28}H_{49}NO_9Na$ $[M+Na]^+$	
Calculated	566.3305
Found	566.3311.

Effect of the Invention

[0104] Novel pseudoerythromycin of the present invention has decreased antibacterial activity and increased anti-inflammatory action, and is expected as the novel antiinflammatory agent.

Claims

1. A novel pseudoerythromycin derivative represented by the general formula [I],



[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

2. A compound according to claim 1 which is de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

3. A compound according to claim 1 which is de(3'-N-methyl)-3' -N-sulfonyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

4. A compound according to claim 1 which is de(3'-N-methyl)-[3'-N-(3-hydroxy-1-propyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

5. A compound according to claim 1 which is de(3'-N-methyl) -3'-N-(2-acetoxyethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

6. A compound according to claim 1 which is de(3'-N-methyl)-3'-N -cyanomethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

7. A compound according to claim 1 which is de(3'-N-methyl)-3'-N - (2-fluoroethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

8. A compound according to claim 1 which is bis-de(3'-N-methyl) -8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

9. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-ethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

10. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-diethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

11. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-allyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

12. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-diallyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

13. A compound according to claimlwhichis bis-de(3'-N-methyl) -3'-N-propargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

14. A compound according to claim 1 which is bis-de(3'-N-methyl) -3',3'-N, N-dipropargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

15. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

16. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dipropyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

17. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-hexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

18. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dihexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemlketal or salt thereof.

19. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-benzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

20. A compound according to claim 1 which is bis-de(3'-N-methyl) -3',3'-N, N-dibenzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

21. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-(2-propyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

22. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-di-(10-bromo-1-decanyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

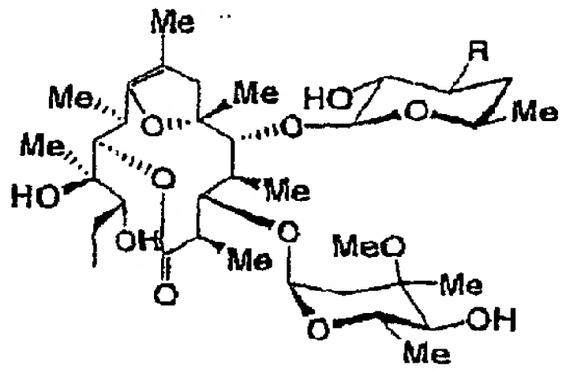
23. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-acetyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

24. The derivative according to claim 1 wherein the compound represented by the general formula [I] has promoting action for differentiation-induction from monocyte to macrophage.

25. The derivative according to claim 1 wherein the compound represented by the general formula [I] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

26. The derivative according to claim 1 wherein the compound represented by the general formula [I] has suppressive effect against pneumonia caused by influenza viral infection.

27. A novel pseudoerythromycin derivative represented by the general formula [II],



[II]

whrein R is heterocyclic containing N which may optionally have substituents, and Me indicates methyl.

28. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-piperidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

29. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-pyrrolidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

30. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-morpholino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

31. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-[hexahydro-1(1H)-azepinyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

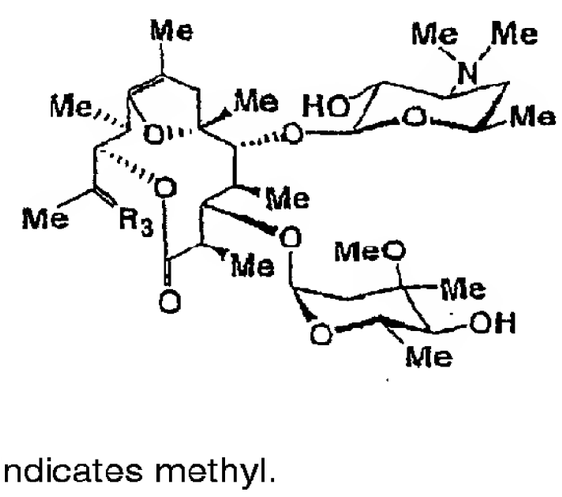
32. The derivative according to claim 27 wherein the compound represented by the general formula [II] has promoting

action for differentiation-induction from monocyte to macrophage.

33. The derivative according to claim 27 wherein the compound represented by the general formula [II] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

34. The derivative according to claim 27 wherein the compound represented by the general formula [II] has suppressive effect against pneumonia caused by influenza viral infection.

35. A novel pseudoerythromycin derivative represented by the general formula [III],



[III]

wherein R_3 is O or NOH, and Me indicates methyl.

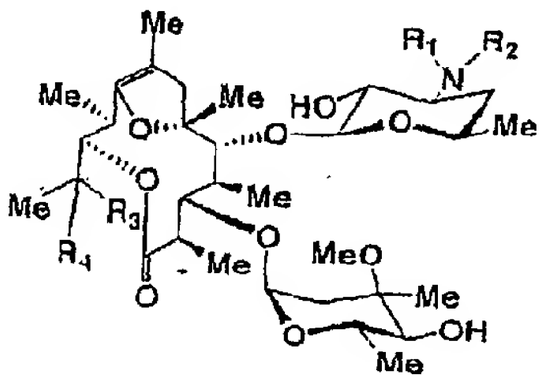
36. A compound according to claim 35 which is de(12-hydroxy) -de[12-(1-hydroxypropyl)]-12-hydroxyoxime-8,9-anhydropseudoerythromycin A 6, 9-hemiketal or salt thereof.

37. The derivative according to claim 35 wherein the compound represented by the general formula [III] has promoting action for differentiation-induction from monocyte to macrophage.

38. The derivative according to claim 35 wherein the compound represented by the general formula [III] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

39. The derivative according to claim 35 wherein the compound represented by the general formula [III] has suppressive effect against pneumonia caused by influenza viral infection.

40. A novel pseudoerythromycin derivative represented by the general formula [IV],



[IV]

whereiin R_1 and R_2 are same or different and each represents H or methyl, R_3 and R_4 represent H, hydroxyl or amino, and Me indicates methyl.

41. A compound according to claim 40 which is de[12-(1-hydroxy propyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

42. A compound according to claim 40 which is de(12-hydroxy) -de[12-(1-hydroxypropyl)]-12-amino-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

43. A compound according to claim 40 which is de(3'-N-methyl)-de [12-(1-hydroxypropyl)]-8, 9-anhydro-pseudo eryth-

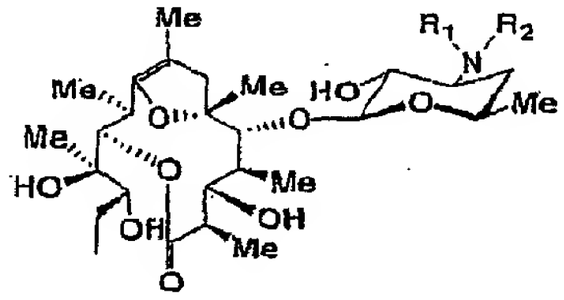
romycin A 6, 9-hemiketal or salt thereof.

44. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has promoting action for differentiation-induction from monocyte to macrophage.

45. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

46. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has suppressive effect against pneumonia caused by influenza viral infection.

47. A novel pseudoerythromycin derivative represented by the general formula [V],



[V]

wherein R_1 and R_2 are same or different and each represents H or methyl, and Me indicates methyl.

48. Acompound according to claim 47 which is de(3-O-cladinosyl) -8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

49. A compound according to claim 47 which is de(3-O-cladinosyl)-de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

50. The derivative according to claim 47 wherein the compound represented by the general formula [V] has promoting action for differentiation-induction from monocyte to macrophage.

51. The derivative according to claim 47 wherein the compound represented by the general formula [V] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

52. The derivative according to claim 47 wherein the compound represented by the general formula [V] has suppressive effect against pneumonia caused by influenza viral infection.

FIG. 1

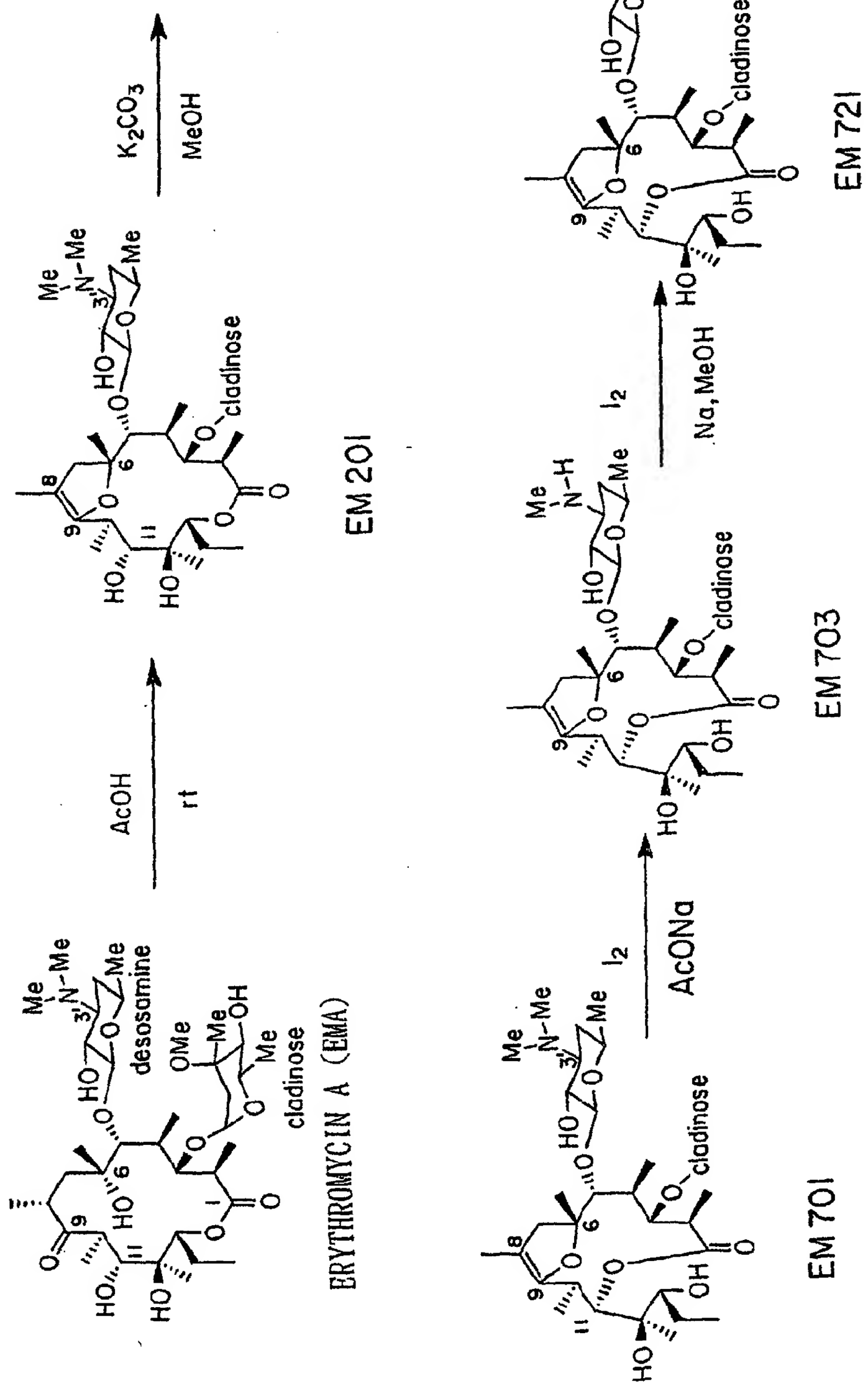
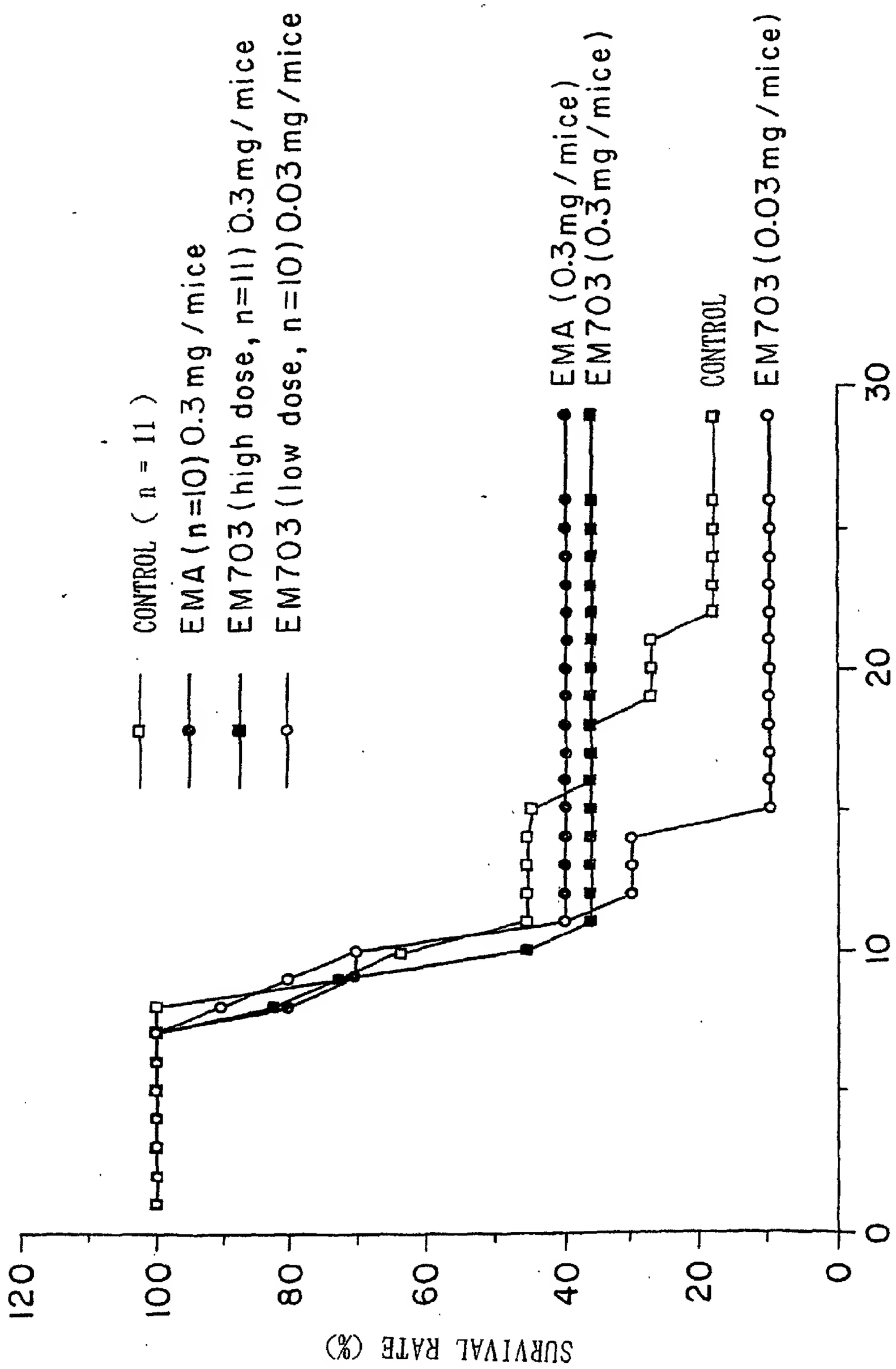

ERYTHROMYCIN A (EMA)
desosamine
cladinose
AcOH
rt
EM 201
EM 721
EM 703
EM 701
K_2CO_3
MeOH
I_2
Na, MeOH
AcONa

FIG. 2


CONTROL (n = 11)
EMA (n=10) 0.3 mg / mice
EM703 (high dose, n=11) 0.3 mg / mice
EM703 (low dose, n=10) 0.03 mg / mice
EMA (0.3mg / mice)
EM703 (0.3 mg / mice)
CONTROL
EM703 (0.03 mg / mice)
120
100
80
60
40
20
0
SURVIVAL RATE (%)
0
10
20
30
DAYS AFTER INFECTION

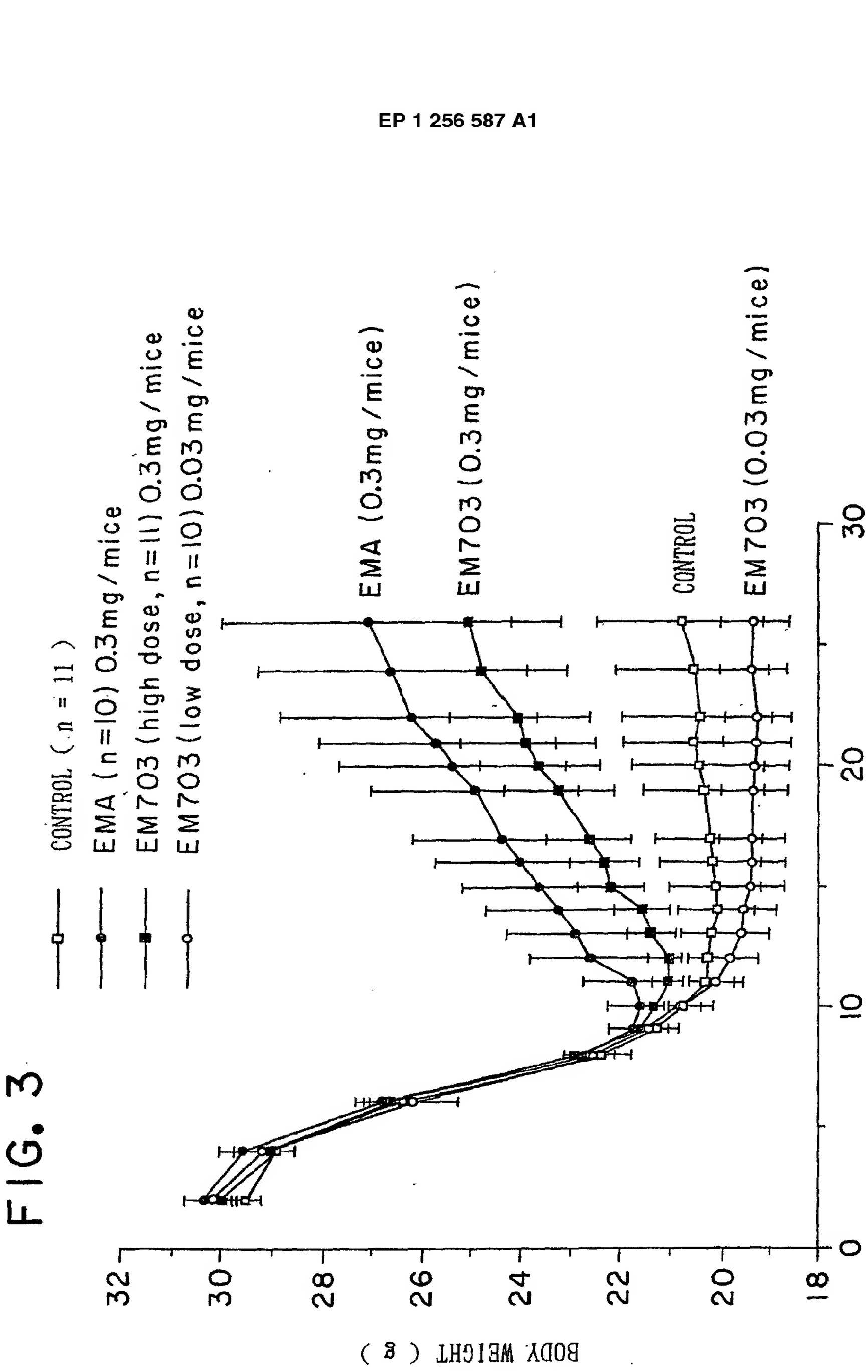

CONTROL (n = 11)
EMA (n=10) 0.3mg / mice
EM703 (high dose, n=10) 0.03 mg / mice
EM703 (low dose, n=10) 0.03 mg / mice
EMA (0.3mg / mice)
EM703 (0.3 mg / mice)
CONTROL
EM703 (0.03mg / mice)
DAYS AFTER INFECTION
BODY WEIGHT (g)
0
10
20
30
18
20
22
24
26
28
30
32

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/05503

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07H17/08 // A61K31/7048, A61P11/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07H17/08 // A61K31/7048, A61P11/00, 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), MEDLINE (STN), EMBASE (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 838469 A (Solvay Pharmaceuticals GmbH), 29 April, 1998 (29.04.98) & DE 19644195 A & US 5912235 A & JP 10-130297 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 128:308701 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1,2,21,24-26 1-52
X Y	EP 550895 A1 (Kali-Chemie Pharma GmbH), 14 July, 1993 (14.07.93) & DE 4200145 A & US 5418224 A & JP 7-247299 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 119:271625 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1,2,21,24-26 1-52

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October, 2000 (24.10.00)	07 November, 2000 (07.11.00)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/05503

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 382472 A2 (Lilly, Eli, and Co.), 16 August, 1990 (16.08.90) & US 5106961 A & JP 2-240095 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 114:102696 especially, compounds of RN:132201-81-1, 121590-61-2, 132137-36-1	35,37-39 1-52
X Y	EP 296717 A2 (Lilly, Eli, and Co.), 28 December, 1988 (28.12.88) & JP, 63-307894, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 111:58271 especially, compounds of RN:105882-69-7, 105882-72-2 121590-61-2	1,24-26,35, 37-39 1-52
X Y	KIBWAGE I.O., et al, "Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus", J. Antibiot, (1987), Vol.40, No.1, pages 1 to 6 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 106:172535 especially, compounds of RN:107745-55-1, 105882-69-7	1,24-26 1-52
X Y	EP 937734 A1 (Solvay Pharmaceuticals G.m.b.H.), 25 August, 1999 (25.08.99) & DE 19805822 A & JP 11-269193 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 131:144790 especially, compounds of RN:236099-91-5,151052-42-5	1,24-26 1-52
X Y	WO 92/18134 A1 (Abbott Laboratories), 29 October, 1992 (29.10.92) & EP 579770 A1 & JP 6-509326 A & US 5538961 A & US 5523418 A & US 5523401 A & US 5554605 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 118:101716 especially, compounds of RN:105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1, 145692-97-3, 145693-00-1, 145693-01-2, 145693-02-3, 145693-03-4, 145774-00-1	1,24-26 1-52
X Y	EP 349100 A2 (Lilly, Eli, and Co.) 03 January, 1990 (03.01.90) & US 4920102 A & JP 1-311096 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 113:59777 especially, compounds of RN:105882-69-7, 127931-39-9, 127966-89-6	1,24-26 1-52

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